10553957

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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	JAN 02	STN pricing information for 2008 now available
NEWS	3	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS	4	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS	5	JAN 28	MARPAT searching enhanced
NEWS	6	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS	7	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS	8	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
NEWS	9	FEB 08	STN Express, Version 8.3, now available
NEWS	10	FEB 20	PCI now available as a replacement to DPCI
NEWS	11	FEB 25	IFIREF reloaded with enhancements
NEWS	12	FEB 25	IMSPRODUCT reloaded with enhancements
NEWS	13	FEB 29	WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification
NEWS	14	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS	15	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS	16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS	17	MAR 31	LPCI now available as a replacement to LDPCI
NEWS	18	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	19	APR 04	STN AnaVist, Version 1, to be discontinued

NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 20 FEBRUARY 2008

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:05:32 ON 10 APR 2008

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THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
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Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 12:06:02 ON 10 APR 2008
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 APR 2008 HIGHEST RN 1013298-21-9
DICTIONARY FILE UPDATES: 9 APR 2008 HIGHEST RN 1013298-21-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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http://www.cas.org/support/stngen/stndoc/properties.html

=>
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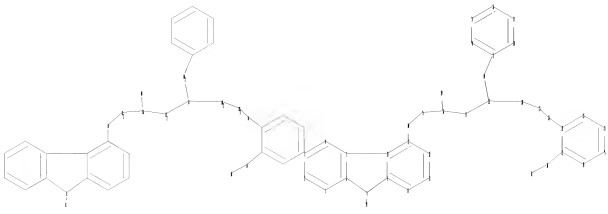

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14 15 16 17 18 26 27 28 29 30 31 32 39
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 20 21 22 23 24 25 33 34 35 36 37 38
chain bonds :
5-18 11-14 14-15 15-16 16-17 16-29 17-32 21-30 22-26 26-27 27-28 28-32 30-31 32-39 33-39
ring bonds :
1-2 1-6 2-3 3-4 4-7 5-6 5-9 6-7 7-10 8-9 8-13 9-10 10-11 11-12 12-13 20-21 20-25 21-22 22-23 23-24 24-25 33-34 33-38 34-35 35-36 36-37 37-38
exact/norm bonds :
5-6 5-9 11-14 16-29 21-30 22-26
exact bonds :
5-18 7-10 14-15 15-16 16-17 17-32 26-27 27-28 28-32 30-31 32-39 33-39
normalized bonds :
1-2 1-6 2-3 3-4 4-7 6-7 8-9 8-13 9-10 10-11 11-12 12-13 20-21 20-25 21-22 22-23 23-24 24-25 33-34 33-38 34-35 35-36 36-37 37-38
isolated ring systems :
containing 1 : 20 : 33 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:CLASS 20:CLASS 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:Atom 34:Atom 35:Atom 36:Atom 37:Atom 38:Atom 39:CLASS

```
L1      STRUCTURE UPLOADED

=> D L1
L1 HAS NO ANSWERS
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> S L1
SAMPLE SEARCH INITIATED 12:06:32 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        8 TO ITERATE

100.0% PROCESSED        8 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            8 TO      329
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> S L1 SSS FULL
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FULL SCREEN SEARCH COMPLETED -      304 TO ITERATE

100.0% PROCESSED      304 ITERATIONS                                6 ANSWERS
SEARCH TIME: 00.00.01

L3            6 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   178.36     178.57

FILE 'HCAPLUS' ENTERED AT 12:06:43 ON 10 APR 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 10 Apr 2008 VOL 148 ISS 15
FILE LAST UPDATED: 9 Apr 2008 (20080409/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> S L3
L4          12 L3

=> S L4 AND DEBENZYLATION
          8545 DEBENZYLATION
            17 DEBENZYLATIONS
          8551 DEBENZYLATION
                 (DEBENZYLATION OR DEBENZYLATIONS)
L5           4 L4 AND DEBENZYLATION

=> S L4 AND CATALYST
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        794377 CATALYSTS
       1020841 CATALYST
                 (CATALYST OR CATALYSTS)
L6           5 L4 AND CATALYST

=> S L5 AND HYDROGENATIOHN
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L7           0 L5 AND HYDROGENATIOHN

=> S L5 AND HYDROGENATION
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        180697 HYDROGENATION
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L8           1 L5 AND HYDROGENATION

=> S L6 AND HYDROGENATION
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          2396 HYDROGENATIONS
        180697 HYDROGENATION
                 (HYDROGENATION OR HYDROGENATIONS)
L9           2 L6 AND HYDROGENATION

=> d 15 ibib abs hitstr tot

L5   ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2006:845541  HCAPLUS
DOCUMENT NUMBER:          145:505330
TITLE:                    Synthesis of carvedilol via method which inhibits
                          formation of impurities
INVENTOR(S):              Byun, Il Suk; Chang, Suk Ku; Kim, Wan Joo; Kim, Young
                          Youn; Lee, Woo Hwa; Oh, Chun Rim; Ryu, Jung Bok
PATENT ASSIGNEE(S):       Chemtech Research Incorporation, S. Korea
SOURCE:                   Repub. Korean Kongkae Taeho Kongbo, No pp. given
                          CODEN: KRXXA7
DOCUMENT TYPE:            Patent
LANGUAGE:                 Korean
```

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2005003764	A	20050112	KR 2003-45256	20030704

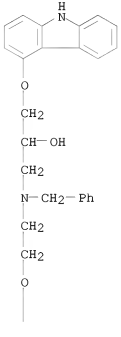
PRIORITY APPLN. INFO.: KR 2003-45256 20030704

AB A method for preparing carvedilol [i.e., 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol] is provided, thereby inhibiting formation of impurities. The highly pure product is useful for the treatment of hypertension. The method for preparing carvedilol thus comprises the reaction of a 1-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanone derivative with 9H-4-hydroxycarbazole. The resulting intermediate then reduced and debenzylated to give the target compound The debenzylation of the reduced intermediate is carried out using a catalyst in presence of base, such as potassium carbonate, sodium carbonate, potassium hydride or sodium hydride.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol via method which inhibits formation of impurities using [(methoxyphenoxy)ethyl]amino]propanone derivative and (hydroxy)carbazole as reactants and reaction sequence involving alkylation, reduction and debenzylation)

RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

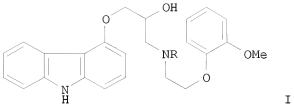
PAGE 1-A



L5 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1260624 HCAPLUS
DOCUMENT NUMBER: 144:22806
TITLE: Process for the preparation of carvedilol
INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113502	A1	20051201	WO 2005-GB1978	20050519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005245182	A1	20051201	AU 2005-245182	20050519
CA 2566197	A1	20051201	CA 2005-2566197	20050519
EP 1756057	A1	20070228	EP 2005-744187	20050519
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2007538061	T	20071227	JP 2007-517424	20050519
IN 2006MN01302	A	20070608	IN 2006-MN1302	20061107
PRIORITY APPLN. INFO.:			GB 2004-11273 A	20040520
			WO 2005-GB1978 W	20050519

OTHER SOURCE(S): CASREACT 144:22806
GI



I

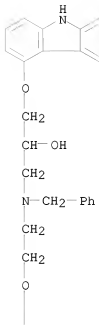
AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004113296	A1	20041229	WO 2004-IN52		20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
IN 2003MU00647	A	20050211	IN 2003-MU647		20030620
US 20060270858	A1	20061130	US 2005-553957		20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647	A	20030620
			IN 2003-MU721	A	20030717
			WO 2004-IN52	W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

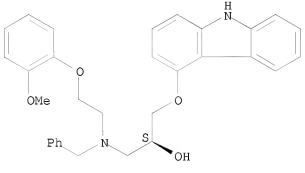
AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 224782-73-4P, (S)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol 224782-76-7P,

(R)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

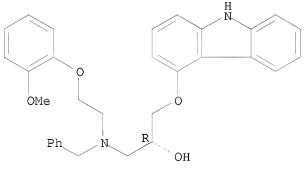
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

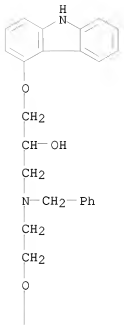
Absolute stereochemistry. Rotation (+).



IT 72955-94-3P, N-Benzylcarvedilol
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747162 HCAPLUS
DOCUMENT NUMBER: 135:288690
TITLE: Intermediates for preparing the R- or S- enantiomer and N-benzyl derivatives of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:

HU 1997-2209	A	19971124
HU 1998-2180	A	19981001
EP 1998-122114	A3	19981124
RU 1998-120700	A	19981118

OTHER SOURCE(S): CASREACT 135:288690

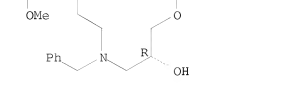
AB R-(+)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and S-(-)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and the R- or S- enantiomer of carvedilol are prepared in high yield and selectivity by the ring-opening cleavage of the resp. R- or S- enantiomer of 4-(oxiranylmethoxy)-9H-carbazole with N-2-[(2'-methoxyphenoxy)ethyl]benzylamine to give the N-benzyl derivs., and the chiral carvedilol enantiomers are prepared by the reductive debenzylation of the resp. chiral N-benzyl derivs. in the presence of Pd/C and hydrazine hydrate.

IT 224782-76-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 224782-76-7 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

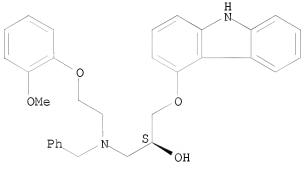
Absolute stereochemistry. Rotation (+).



IT 224782-73-4DP, acid-addition salts 224782-73-4P
224782-76-7DP, acid-addition salts
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

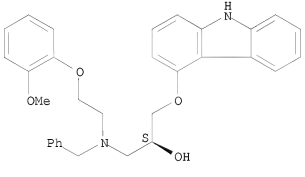
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



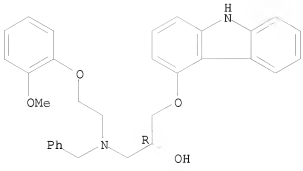
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



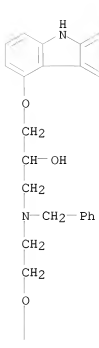
=> d l6 ibib abs hitstr tot

L6 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:397789 HCAPLUS
DOCUMENT NUMBER: 148:239026
TITLE: A cost effective process for production of carvedilol
INVENTOR(S): Shankar, Sanganabhatla; Pandurang, Suryavanshi Jitendra; Moorthy, Koduru Ramanarasimha
PATENT ASSIGNEE(S): Wanbury Limited, India
SOURCE: Indian Pat. Appl., 8pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006MU00771	A	20060825	IN 2006-MU771	20060522

PRIORITY APPLN. INFO.: IN 2006-MU771 20060522
OTHER SOURCE(S): CASREACT 148:239026
AB A cost effective process for preparation of highly pure carvedilol substantially free from impurities is described herein; 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol is catalytically hydrogenated using inexpensive catalyst like Raney Nickel and isolating crude carvedilol free from penultimate and other major impurity; which is purified in an Et acetate/methyl Et ketone to obtain pure Carvedilol.
IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(a cost effective process for production of carvedilol)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L6 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:845541 HCAPLUS
DOCUMENT NUMBER: 145:505330
TITLE: Synthesis of carvedilol via method which inhibits formation of impurities
INVENTOR(S): Byun, Il Suk; Chang, Suk Ku; Kim, Wan Joo; Kim, Young Youn; Lee, Woo Hwa; Oh, Chun Rim; Ryu, Jung Bok
PATENT ASSIGNEE(S): Chemtech Research Incorporation, S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2005003764	A	20050112	KR 2003-45256	20030704

PRIORITY APPLN. INFO.: KR 2003-45256 20030704

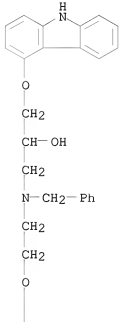
AB A method for preparing carvedilol [i.e., 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol] is provided, thereby inhibiting formation of impurities. The highly pure product is useful for the treatment of hypertension. The method for preparing carvedilol thus comprises the reaction of a 1-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanone derivative with 9H-4-hydroxycarbazole. The resulting intermediate then reduced and debenzylated to give the target compound The debenzylation of the reduced intermediate is carried out using a catalyst in presence of base, such as potassium carbonate, sodium carbonate, potassium hydride or sodium hydride.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol via method which inhibits formation of impurities using [(methoxyphenoxy)ethyl]amino]propanone derivative and (hydroxy)carbazole as reactants and reaction sequence involving alkylation, reduction and debenzylation)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



L6 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 20060270858	A1	20061130	US 2005-553957	20051019

PRIORITY APPLN. INFO.:
IN 2003-MU647 A 20030620
IN 2003-MU721 A 20030717
WO 2004-IN52 W 20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof

with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the

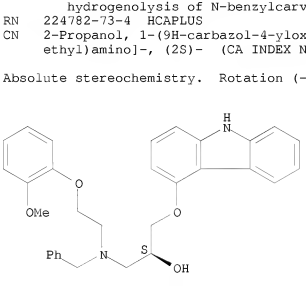
product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 224782-73-4P, (S)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol 224782-76-7P, (R)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 224782-73-4 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

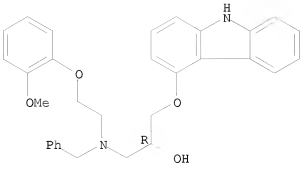
Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS

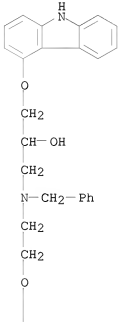
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 72955-94-3P, N-Benzylcarvedilol
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
JP 4056883	B2	20080305		
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 20040127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:			
	EP 2001-101584	A	20010125
	US 2002-54462	A3	20020122
	WO 2002-EP583	W	20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

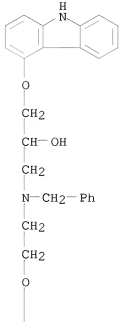
AB A process for the preparation heterocyclic indene analogs, especially with the preparation
of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and
high catalyst loadings.

IT 72955-94-3P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A

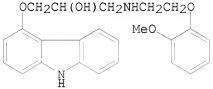


PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:270010 HCAPLUS
DOCUMENT NUMBER: 120:270010
TITLE: Synthesis of the enantiomers and three racemic metabolites of Carvedilol labeled to high specific activity with tritium
AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.; Garnes, K. T.; Heys, J. R.
CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1993), 33(12), 1091-105
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

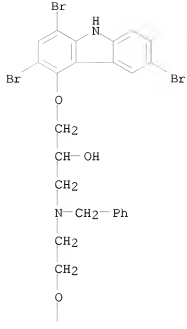
AB Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate, 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.

IT 154582-54-4P 154582-58-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate in preparation of tritium labeled Carvedilol)

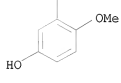
RN 154582-54-4 HCAPLUS

CN Phenol, 3-[2-[[2-hydroxy-3-[(1,3,6-tribromo-9H-carbazol-4-yl)oxy]propyl](phenylmethyl)amino]ethoxy]-4-methoxy- (CA INDEX NAME)

PAGE 1-A

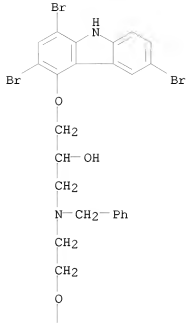


PAGE 2-A

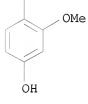


RN 154582-58-8 HCAPLUS
CN Phenol, 4-[2-[[2-hydroxy-3-[(1,3,6-tribromo-9H-carbazol-4-yl)oxy]propyl](phenylmethyl)amino]ethoxy]-3-methoxy- (CA INDEX NAME)

PAGE 1-A

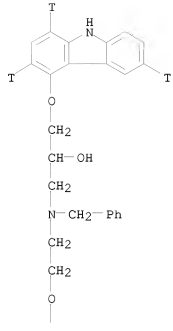


PAGE 2-A

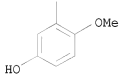


IT 154582-61-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 154582-61-3 HCAPLUS
CN Phenol, 3-[2-[[3-(9H-carbazol-4-yl-1,3,6-t3-oxy)-2-hydroxypropyl](phenylmethyl)amino]ethoxy]-4-methoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004113296	A1	20041229	WO 2004-IN52		20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
IN 2003MU00647	A	20050211	IN 2003-MU647		20030620
US 20060270858	A1	20061130	US 2005-553957		20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647	A	20030620
			IN 2003-MU721	A	20030717
			WO 2004-IN52	W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

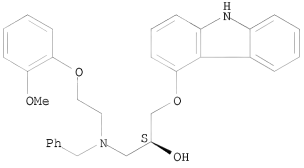
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).
IT 224782-73-4P, (S)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-

3-[(9H-carbazol-4-yl)oxy]propan-2-ol 224782-76-7P,
(R)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

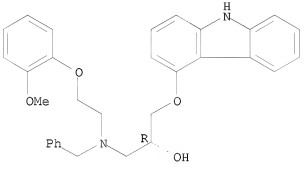
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

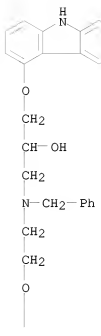
Absolute stereochemistry. Rotation (+).



IT 72955-94-3P, N-Benzylcarvedilol
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:397789 HCAPLUS
DOCUMENT NUMBER: 148:239026
TITLE: A cost effective process for production of carvedilol
INVENTOR(S): Shankar, Sanganabhatla; Pandurang, Suryavanshi Jitendra; Moorthy, Koduru Ramanarasimha
PATENT ASSIGNEE(S): Wanbury Limited, India
SOURCE: Indian Pat. Appl., 8pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006MU00771	A	20060825	IN 2006-MU771	20060522

PRIORITY APPLN. INFO.: IN 2006-MU771 20060522

OTHER SOURCE(S): CASREACT 148:239026

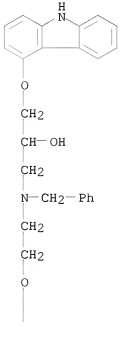
AB A cost effective process for preparation of highly pure carvedilol substantially free from impurities is described herein; 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol is catalytically hydrogenated using inexpensive catalyst like Raney Nickel and isolating crude carvedilol free from penultimate and other major impurity; which is purified in an Et acetate/methyl Et ketone to obtain pure Carvedilol.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(a cost effective process for production of carvedilol)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



L9 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 20060270858	A1	20061130	US 2005-553957	20051019

PRIORITY APPLN. INFO.:
IN 2003-MU647 A 20030620
IN 2003-MU721 A 20030717
WO 2004-IN52 W 20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof

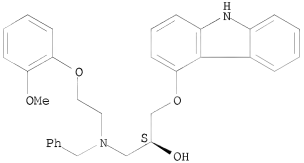
with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 224782-73-4P, (S)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol 224782-76-7P, (R)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 224782-73-4 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

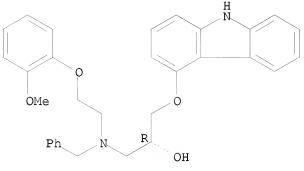
Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS

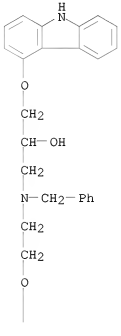
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 72955-94-3P, N-Benzylcarvedilol
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



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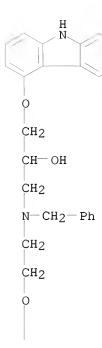
L4 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:397789 HCAPLUS
DOCUMENT NUMBER: 148:239026
TITLE: A cost effective process for production of carvedilol
INVENTOR(S): Shankar, Sanganabhatla; Pandurang, Suryavanshi Jitendra; Moorthy, Koduru Ramanarasimha
PATENT ASSIGNEE(S): Wanbury Limited, India
SOURCE: Indian Pat. Appl., 8pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2006MU00771	A	20060825	IN 2006-MU771	20060522

PRIORITY APPLN. INFO.: IN 2006-MU771 20060522
OTHER SOURCE(S): CASREACT 148:239026
AB A cost effective process for preparation of highly pure carvedilol substantially free from impurities is described herein; 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol is catalytically hydrogenated using inexpensive catalyst like Raney Nickel and isolating crude carvedilol free from penultimate and other major impurity; which is purified in an Et acetate/methyl Et ketone to obtain pure Carvedilol.
IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(a cost effective process for production of carvedilol)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



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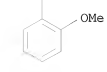


L4 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:845541 HCAPLUS
DOCUMENT NUMBER: 145:505330
TITLE: Synthesis of carvedilol via method which inhibits formation of impurities
INVENTOR(S): Byun, Il Suk; Chang, Suk Ku; Kim, Wan Joo; Kim, Young Youn; Lee, Woo Hwa; Oh, Chun Rim; Ryu, Jung Bok
PATENT ASSIGNEE(S): Chemtech Research Incorporation, S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2005003764	A	20050112	KR 2003-45256	20030704

PRIORITY APPLN. INFO.: KR 2003-45256 20030704

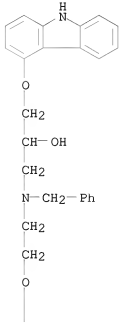
AB A method for preparing carvedilol [i.e., 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol] is provided, thereby inhibiting formation of impurities. The highly pure product is useful for the treatment of hypertension. The method for preparing carvedilol thus comprises the reaction of a 1-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanone derivative with 9H-4-hydroxycarbazole. The resulting intermediate then reduced and debenzylated to give the target compound The debenzylation of the reduced intermediate is carried out using a catalyst in presence of base, such as potassium carbonate, sodium carbonate, potassium hydride or sodium hydride.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol via method which inhibits formation of impurities using [(methoxyphenoxy)ethyl]amino]propanone derivative and (hydroxy)carbazole as reactants and reaction sequence involving alkylation, reduction and debenzylation)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A

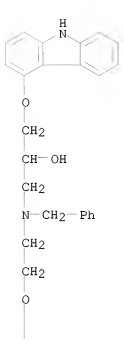


L4 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1338355 HCAPLUS
DOCUMENT NUMBER: 144:419905
TITLE: Determination of carvedilol and its impurities in pharmaceuticals
AUTHOR(S): Stojanovic, J.; Marinkovic, V.; Vladimirov, S.; Velickovic, D.; Sibinovic, P.
CORPORATE SOURCE: 'Zdravlje-Actavis', Pharmaceutical and Chemical Industry, Leskovac, 16000,
SOURCE: Chromatographia (2005), 62(9/10), 539-542
CODEN: CHRGB7; ISSN: 0009-5893
PUBLISHER: Vieweg Verlag/GWV Fachverlage GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A reversed-phase high-performance liquid chromatog. (RP-HPLC) method was developed for separation of carvedilol and its impurities from Karvileks tablets. The best separation was achieved on a 100 mm + 4.6 mm, 5 μm particle size, Chromolit RP 8e column. Use of acetonitrile-water, 45:55 (volume/volume), adjusted to pH 2.5 with formic acid, as mobile phase at a flow rate of 0.5 mL min-1 enabled acceptable resolution of carvedilol, in large excess, from possible impurities, in a short elution time. UV detection was performed at 280 nm. Linearity, accuracy, precision, selectivity, and robustness were validated and found to be satisfactory. Overall, the proposed method was found to be highly sensitive, suitable, and accurate for quant. determination of carvedilol and its impurities in dosage forms and in raw materials.

IT 72955-94-3
RL: ANT (Analyte); FMU (Formation, unclassified); ANST (Analytical study); FORM (Formation, nonpreparative)
(determination of carvedilol and its impurities in pharmaceuticals)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1260624 HCAPLUS
DOCUMENT NUMBER: 144:22806
TITLE: Process for the preparation of carvedilol
INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra
PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2005113502	A1	20051201	WO 2005-GB1978		20050519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
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IN 2006MN01302	A	20070608	IN 2006-MN1302		20061107
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			WO 2005-GB1978	W	20050519

OTHER SOURCE(S): CASREACT 144:22806

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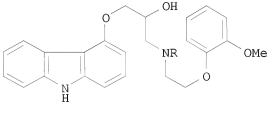


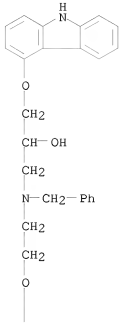
I

AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1128799 HCAPLUS
DOCUMENT NUMBER: 143:386916
TITLE: An improved process for the manufacture of carvedilol
INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj Ramchandra
PATENT ASSIGNEE(S): Cipla Ltd., India
SOURCE: Indian, 11 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-BO583	19990817
PRIORITY APPLN. INFO.:			IN 1999-BO583	19990817

OTHER SOURCE(S): CASREACT 143:386916; MARPAT 143:386916
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

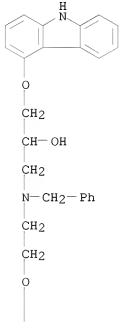
AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [R1 = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IV]. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [R1 = Ch2Ph] afforded carvedilol I.

IT 72955-94-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(improved process for the manufacture of carvedilol)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



L4 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1154673 HCAPLUS
DOCUMENT NUMBER: 142:93675
TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar
PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113296	A1	20041229	WO 2004-IN52	20040304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IN 2003MU00647	A	20050211	IN 2003-MU647	20030620
US 20060270858	A1	20061130	US 2005-553957	20051019
PRIORITY APPLN. INFO.:			IN 2003-MU647 A	20030620
			IN 2003-MU721 A	20030717
			WO 2004-IN52 W	20040304

OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer

or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the

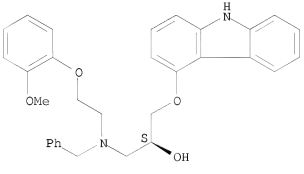
product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 224782-73-4P, (S)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol 224782-76-7P, (R)-1-[N-Benzyl-N-[2-(2-methoxyphenoxy)ethyl]amino]-3-[(9H-carbazol-4-yl)oxy]propan-2-ol
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 224782-73-4 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

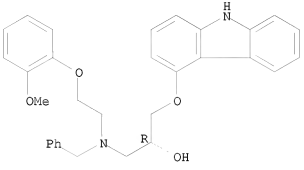
Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS

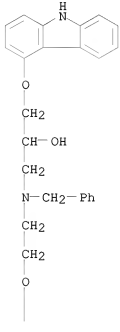
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 72955-94-3P, N-Benzylcarvedilol
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:556143 HCAPLUS
DOCUMENT NUMBER: 137:125080
TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and catalyst loading
INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert
PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.
SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

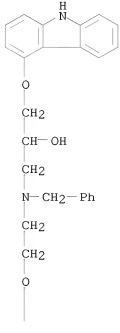
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020099223	A1	20020725	US 2002-54462	20020122
US 6777559	B2	20040817		
CA 2434408	A1	20020801	CA 2002-2434408	20020122
WO 2002059089	A2	20020801	WO 2002-EP583	20020122
WO 2002059089	A3	20021031		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002247645	A1	20020806	AU 2002-247645	20020122
EP 1355880	A2	20031029	EP 2002-716673	20020122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519465	T	20040702	JP 2002-559391	20020122
JP 4056883	B2	20080305		
IN 2003CN01126	A	20050422	IN 2003-CN1126	20030722
MX 2003PA06606	A	20030922	MX 2003-PA6606	20030723
US 20040127723	A1	20040701	US 2004-763296	20040122
US 7169935	B2	20070130		

PRIORITY APPLN. INFO.:			
	EP 2001-101584	A	20010125
	US 2002-54462	A3	20020122
	WO 2002-EP583	W	20020122

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080
AB A process for the preparation heterocyclic indene analogs, especially with the preparation

of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and
high catalyst loadings.
IT 72955-94-3P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)
RN 72955-94-3 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747162 HCAPLUS
DOCUMENT NUMBER: 135:288690

TITLE: Intermediates for preparing the R- or S- enantiomer and N-benzyl derivatives of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol]

INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter

PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.

SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:
HU 1997-2209 A 19971124
HU 1998-2180 A 19981001
EP 1998-122114 A3 19981124
RU 1998-120700 A 19981118

OTHER SOURCE(S): CASREACT 135:288690

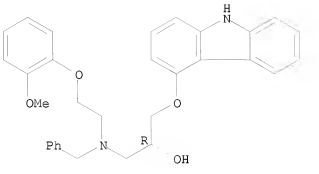
AB R-(+)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and S-(-)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and the R- or S- enantiomer of carvedilol are prepared in high yield and selectivity by the ring-opening cleavage of the resp. R- or S- enantiomer of 4-(oxiranylmethoxy)-9H-carbazole with N-2-[(2'-methoxyphenoxy)ethyl]benzylamine to give the N-benzyl derivs., and the chiral carvedilol enantiomers are prepared by the reductive debenzylation of the resp. chiral N-benzyl derivs. in the presence of Pd/C and hydrazine hydrate.

IT 224782-76-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 224782-76-7 HCAPLUS

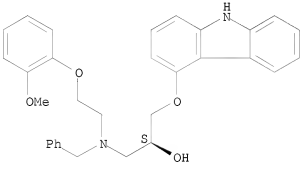
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



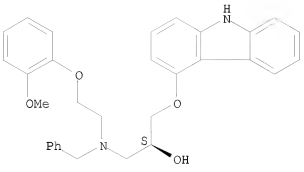
IT 224782-73-4DP, acid-addition salts 224782-73-4P
224782-76-7DP, acid-addition salts
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs. of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



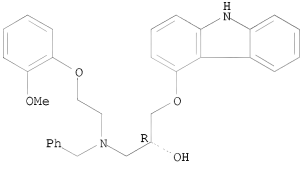
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 224782-76-7 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylm
ethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:747161 HCAPLUS
DOCUMENT NUMBER: 135:288689
TITLE: Process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-ol [carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:	HU 1997-2209	A 19971124
	HU 1998-2180	A 19981001
	EP 1998-122114	A3 19981124
	RU 1998-120700	A 19981118

OTHER SOURCE(S): CASREACT 135:288689

AB A process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)-ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzyl-2'-[{(2'-methoxy-phenoxy)ethyl}amino]-3-propan-2-ol is reacted with 4-hydroxy-9H-carbazole and the resulting 1-N-benzyl-2'-(methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the 1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-{2}-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

IT 72955-94-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

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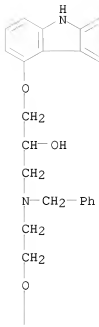

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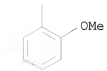

L4 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:344783 HCAPLUS
DOCUMENT NUMBER: 130:352184
TITLE: Preparation of carvedilol
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 918055	A1	19990526	EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 9802180	A1	20001228	HU 1998-2180	19981001
CZ 296521	B6	20060412	CZ 1998-3561	19981104
CZ 297445	B6	20061213	CZ 2004-1111	19981104
HR 980590	B1	20031231	HR 1998-590	19981112
SK 284109	B6	20040908	SK 1998-1560	19981112
RU 2216539	C2	20031120	RU 1998-120700	19981118
RU 2245875	C2	20050210	RU 2003-107772	19981118
EP 1142873	A2	20011010	EP 2001-111213	19981124
EP 1142873	A3	20030910		
EP 1142873	B1	20040421		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES, FR, GB, IT, SI, LT, LV, RO				
ES 2196459	T3	20031216	ES 1998-122114	19981124
ES 2221875	T3	20050116	ES 2001-111213	19981124

PRIORITY APPLN. INFO.:

HU 1997-2209	A	19971124
HU 1998-2180	A	19981001
RU 1998-120700	A	19981118
EP 1998-122114	A3	19981124

AB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9H-carbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.

IT 72955-94-3P 224782-73-4P 224782-76-7P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carvedilol)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

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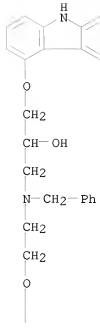

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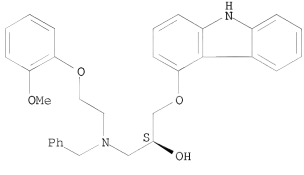
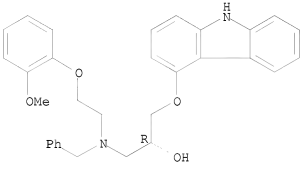
RN 224782-73-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



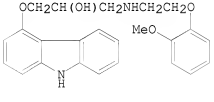
RN 224782-76-7 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:270010 HCAPLUS
DOCUMENT NUMBER: 120:270010
TITLE: Synthesis of the enantiomers and three racemic metabolites of Carvedilol labeled to high specific activity with tritium
AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.; Garnes, K. T.; Heys, J. R.
CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1993), 33(12), 1091-105
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were

polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate, 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.

IT 154582-54-4P 154582-58-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate in preparation of tritium labeled Carvedilol)

RN 154582-54-4 HCAPLUS

CN Phenol, 3-[2-[[2-hydroxy-3-[(1,3,6-tribromo-9H-carbazol-4-yl)oxy]propyl](phenylmethyl)amino]ethoxy]-4-methoxy- (CA INDEX NAME)

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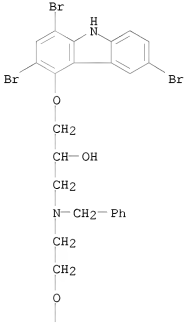

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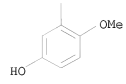

RN 154582-58-8 HCAPLUS
CN Phenol, 4-[2-[[2-hydroxy-3-[(1,3,6-tribromo-9H-carbazol-4-yl)oxy]propyl](phenylmethyl)amino]ethoxy]-3-methoxy- (CA INDEX NAME)

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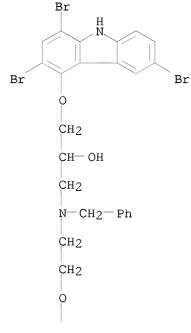

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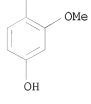

IT 154582-61-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 154582-61-3 HCAPLUS

CN Phenol, 3-[2-[[3-(9H-carbazol-4-yl-1,3,6-t3-oxy)-2-hydroxypropyl](phenylmethyl)amino]ethoxy]-4-methoxy- (9CI) (CA INDEX NAME)

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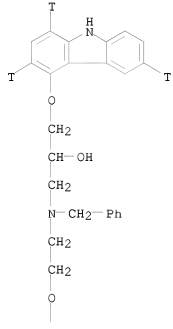

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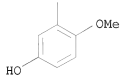


L4 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1980:128716 HCAPLUS
DOCUMENT NUMBER: 92:128716
ORIGINAL REFERENCE NO.: 92:20983a,20986a
TITLE: Carbazolyl-4-oxypropanolamine derivatives
INVENTOR(S): Wiedemann, Fritz; Kampe, Wolfgang; Thiel, Max; Sponer, Gisbert; Roesch, Egon; Dietmann, Karl
PATENT ASSIGNEE(S): Boehringer Mannheim G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 27 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2815926	A1	19791018	DE 1978-2815926	19780413
CA 1129416	A1	19820810	CA 1979-324667	19790402
DK 7901419	A	19791014	DK 1979-1419	19790406
DK 154555	B	19881128		
DK 154555	C	19890619		
FI 7901142	A	19791014	FI 1979-1142	19790406
FI 70406	B	19860327		
FI 70406	C	19860912		
AU 7945820	A	19791018	AU 1979-45820	19790406
AU 522975	B2	19820708		
ES 479396	A1	19800416	ES 1979-479396	19790406
SU 810079	A3	19810228	SU 1979-2745301	19790406
EP 4920	A1	19791031	EP 1979-101063	19790407
EP 4920	B1	19810805		
R: BE, CH, DE, FR, GB, IT, LU, NL, SE				
IL 57020	A	19820730	IL 1979-57020	19790408
DD 143607	A5	19800903	DD 1979-212096	19790409
CS 227007	B2	19840416	CS 1979-2434	19790410
JP 54157558	A	19791212	JP 1979-43119	19790411
JP 01023462	B	19890502		
ZA 7901732	A	19800528	ZA 1979-1732	19790411
HU 21840	A2	19820227	HU 1979-BO1774	19790412
HU 179433	B	19821028		
AT 7902762	A	19840115	AT 1979-2762	19790412
AT 375639	B	19840827		
CS 227047	B2	19840416	CS 1982-6106	19820820
US 4503067	A	19850305	US 1983-479921	19830404
JP 63258416	A	19881025	JP 1987-76548	19870331
PRIORITY APPLN. INFO.:			DE 1978-2815926 A	19780413
			US 1979-21394 A1	19790316
			CS 1979-2434 A3	19790410
			US 1980-198975 A1	19801021
OTHER SOURCE(S):		MARPAT 92:128716		

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

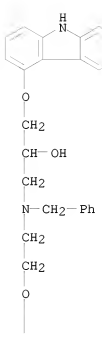
AB A wide range of I (R = H, lower alkyl, or aroyl; R1 = H, lower alkyl, or aralkyl, R2 and R3 independently were H or lower alkyl, X = CH2, O, S, or valence bond; Ar = mono- or bicyclic aryl or pyridyl) (.apprx.50 compds.) were prepared as β-sympatholytics and vasodilators (no data), in most cases by reaction of 4-(oxiranylmethoxy)carbazole (II) with an amine. Thus, 6.0 g II and 7.6 g 2-MeOC6H4CH2CH2NH2 were stirred 20 h at 70° to give 61% III. Also prepared were, e.g., IV and V.

IT 72955-94-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acetylation of)

RN 72955-94-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl](phenylmethyl)amino]- (CA INDEX NAME)

PAGE 1-A



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=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	160.39	338.96
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-19.20	-19.20

STN INTERNATIONAL LOGOFF AT 12:13:33 ON 10 APR 2008